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10/573,227	03/24/2006	Julie A. Dixon	5178	4978

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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,227	DIXON ET AL.	
	Examiner	Art Unit	
	/Venkataraman Balasubramanian/	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response, which included amendment to claim 1, filed on 11/19/2008, is made of record. Claims 1-11 are pending. In view of applicants' response, the 112 first paragraph rejection of claims 1-11 as pertaining to scope of enablement of solvate has been obviated. However, the following rejections made in the previous office action are maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10 and 11 are rejected under U.S.C. 112, first paragraph, because the specification while being enabling for treating breast cancer does not reasonably provide enablement for treating any or all hyperproliferative disorder and any or all cancer, as generically embraced in these claims. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims.

The instant method of use claims 10 and 11 are drawn to treating a disease hyperproliferative disorder and treating cancer, by inhibiting cell proliferation in general .

Instant claims, as recited, are reach through claims. A reach through claim is a claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through a scope of invention for which they lack adequate written description and enabling disclosure in the specification.

In the instant case, based on the inhibition of cell proliferation by imparting cytotoxicity by the instant compounds, instant claims reaches through inhibiting and treating any or all diseases in general and thereby they lack adequate written description and enabling disclosure in the specification.

The scope of the claims involves all of the millions of compounds of claim 1 as well as the thousand of diseases embraced by the terms proliferative disorder and cancer.

Proliferative disease would include benign tumors, malignant tumors, polyps, lumps, lesions, other pre-cancerous conditions, psoriasis, leukemia, the hyper proliferation of the gastric epithelium caused by the Helicobacter pylori infection of ulcers.

Cancer is just an umbrella term. Tumors vary from those so benign that they are never treated to those so virulent that all present therapy is useless. Accordingly, treatments for cancer are normally tailored to the particular type of cancer present, as there is no, and there can be no “magic bullet” against cancer generally.

Thus, the scope of claims is extremely broad.

More specifically, in the instant case, based on the mode of action of instant compounds as inhibitor of cell proliferation, based on limited assay, it is claimed that i treating any or all hyperproliferative disorders including any or all cancers in general, for which there is no enabling disclosure. The scope of the claims includes any or all cancer based on the mode of action of the compound of instant claims for which there are no enabling disclosure. In addition, the scope of these claims as recited would

include treatment of various cancers such as lung cancer, bone cancer, pancreatic cancer, skin cancer. cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region. stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers, which is not adequately enabled solely based on the activity of the compounds provided in the specification.

Moreover many if not most of diseases such as psoriasis, lung cancer, brain cancer, pancreatic cancer, colon cancer etc. are very difficult to treat and despite the fact that there are many anticancer drugs.

The instant compounds are disclosed to have receptor tyrosine kinase inhibitory activity and it is recited that the instant compounds are therefore useful in treating any or all diseases stated above for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as cell proliferation inhibitor that would be useful for all sorts of

proliferative diseases and cancers. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host.

The scope of the invention includes millions of compounds of claim 1 as well as the thousand and thousand of diseases embraced by the terms recited above.

No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a “compound” is contrary to our present understanding of oncology. Cecil Textbook of Medicine states, “each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study” (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body.

Also see the PTO website

<<http ://www.uspto.gov/web/offices/pac/dapp/1 pecba.htm#7>>

ENABLEMENT DECISION TREE, Example F, situation 1) which is directed to the scope of cancers.

Also, note MPEP 2164.08(b) which states that claims that read on "... significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative.". Clearly that is the case here.

Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Denny, Expert Opin.Emerg.Drugs, Vol. 9(1), 105-133 (2004), Wood et al., Current Opinion in Pharmacology, 1, 370377, 2001. See also Mass, R. D., Int. J. Radiation Oncology Bio. Phys. Vol. 58(3): 932-940, 2004 and Fabbro et al. Pharmacology & therapeutics 93, 79-98, 2002. Also see Malumbres et al., Trends in Biochemical Sciences, 30(11), 630-641, 2005., Lolli et al., Cell Cycle 4 :4, 572-577, 2005., Sherr et al., Genes & Development 18, 2699-2711, 2004., Fischer Cell Cycle 3:6, 742-746, 2004. Note Malumbres indicates CDK2 gene is dispensable and mice without CDK2 are normal. Sherr also states the without he said gene much of the fetal development occurs normally. Also note Fischer states" recent findings, however, suggest that CDK2 may not be the key cell cycle player previously assumed, after all, It has now become clear that CDKs have functions in physiological processes

other than coordination of cell cycle progression, particularly regulation of DNA transcription." Thus, cell proliferation by various mode of action is still exploratory and requires further exeperimentation.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating hyperproliferative disorders/diseases that require inhibition of cell proliferation due to cytotoxicity activity.

2) The state of the prior art: A publication expressed that the protein kinase inhibition effects are unpredictable and are still exploratory. See Denny, Wood, Mass, R. D., and Fabbro et al., Malumbres et al., Sherr et al., Lolli et al., and Fischer et al., cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all hyperproliferative disorders including all cancers and the state of the art is that the effects of cell proliferation inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace use of a huge genus of compounds and any or all proliferative diseases and cancers .

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as “sufficient working examples”, “the level of skill in the art” and “predictability”, etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, “A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” That conclusion

is clearly justified here and undue experimentation will be required to practice Applicants' invention.

This rejection is same as made in the previous office action. Applicants' traversal is not persuasive. As noted above, instant claims are reach through claims. Based on the limited in vitro assays cited in the specification, instant claims reach through treating various proliferative diseases for which there is no adequate enabling disclosure.

Applicants have not provided in direct evidence for scope o enablement or non-patent literature to support for the full scope claimed in the above stated claims.

Contrary to applicants' urging citing In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970), as noted above one need to unduly extensive experimentation to identify which disease is treatable.

Several case laws do not support applicants' contention of treating any or all diseases based on mode of action alone.

The issue in Ex parte Balzarini 21 USPQ2d 1892 concerned HIV treatment and the Board of Patent Appeals and Interferences wrote "While the in vitro testing performed on these anti-viral compounds appears to be useful as a screening tool in order to determine which of these anti-viral compounds are candidates for further testing to determine if they possess in vivo utility, the in vitro tests were not predictive of in vivo efficacy."

The issue in Fujikawa v. Wattanasin 39 USPQ2d 1895 was adequacy of in vitro testing of inhibitors of cholesterol biosynthesis and U.S. Court of Appeals Federal Circuit wrote, "in vitro results, in combination with a known correlation between such in

vitro results and in vivo activity, may be sufficient to establish practical utility". Such a correlation does not exist in the art of cancer therapy employing CDK2 inhibitors.

In a peripheral issue involving assaying insulin-like growth factor-I ("IGF- I") in Genentech Inc. v. Chiron Corp. 55 USPQ2d 1636, U.S. Court of Appeals Federal Circuit wrote "by the critical date, ... [s]pecific binding in an RRA was known by those skilled in the art to be reasonably correlated with the in vivo biological activity of IGF-I."

In Ex parte Bhide 42 USPQ2d 1441, the Board of Patent Appeals and Interferences wrote "While in vitro or in vivo tests would not be the only possible way to overcome our basis for questioning applicants' utility, in vitro or in vivo tests certainly would provide relevant evidence". The issue in the present case is not the utility of applicants' compounds, which was at issue in Ex parte Bhide 42 USPQ2d 1441, but rather the narrower issue of enablement for claims drawn to the treatment of all cancers. Since such a claim is inherently not credible, the standard of proof required for such an assertion must be high.

In a case concerning a DNA sequence encoding a mature human IL-3 protein, Ex parte Anderson 30 USPQ2d 1866, the Board of Patent Appeals and Interferences wrote in passing "We question whether one skilled in the art would accept appellants' in vitro test as predictive of in vivo results and whether one skilled in the art would know how to use the Pro (8) protein made .... Should the claims of this application be prosecuted further in a continuing application we urge the examiner to consider the enablement and utility aspects of patentabilityi" In an anti-tumor application, Ex parte Aggarwal 23 USPQ2d 1334, the Board of Patent Appeals and Interferences wrote

"there is considerable doubt that those skilled in the art would be willing to accept appellants' in vitro tests and in vivo tests as established models predictive of utility against tumors in humans. See In re Jolles, 628 F.2d 1322, 206 USPQ 885 The examiner had more than adequate reason to doubt the objective truth of the broad statement of utility set forth in appellants' specification." In the most definitive finding on this issue of the adequacy of in vitro assays for clinical claims, Ex parte Stevens 16 USPQ2d 1379 the Board of Patent Appeals and Interferences wrote "The examiner's position is based on the supposition that the facts described above evidence a prima facie case of nonenablement with regard to the disclosed utility in light of all the applicable legal precedents. Where as here, the disclosed utility is the treatment of cancer, we agree with this supposition. The examiner has cited Ex parte Busse, 1 USPQ2d 1908. In that case, the Board of Patent Appeals and Interferences reviewed the relevant prior decisions of its reviewing court. We shall not repeat those citations here. Suffice it to say that in every cited case the narrow issue involved was whether or not the evidence of record was based on in vivo or in vitro studies which were generally recognized by those of ordinary skill in the art as being reasonably predictive of success in the practical utility under consideration, i.e., human or, at least, mammalian therapy."

In a vaccine case, Ex parte Maas 14 USPQ2d 1762, the Board of Patent Appeals and Interferences wrote "First, although appellants' specification describes certain in vitro experiments, there is no correlation on this record between in vitro experiments and a practical utility in currently available form for humans or animals. It is not enough to rely on in vitro studies where, as here, a person having ordinary skill in the art has no

basis for perceiving those studies as constituting recognized screening procedures with clear relevance to utility in humans or animals. The burden is on appellants to establish the significance of the in vitro experiments set forth in their specification."

Moreover, the specification does not enable any physician skilled in the art of medicine, to use the compound of the invention commensurate in scope with the claims. The specification does not describe administration procedures and ranges of dosage regimen. The method of administration and/or the dose levels depend on a number of factors, which have to be evaluated by one of ordinary skill in the art. These factors include a) determining which of the claimed compounds would treat any particular claimed disease; b) synthesize the compound; c) formulate into a suitable dosage form depending the type of administration method; and d) conduct clinical trials or test the compound in an assay known to be correlated to clinical efficacy of such treatment. The specification provide assays to determine the activity of the compounds and nothing more. Applicants have not asserted that it is art recognized that the assays are correlated to clinical efficacy for treatment of all indications. Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of in vivo efficacy by those skilled in the art. See for example In re Ruskin 148 USPQ 221; Exparte Jovanovics 211 USPQ 907. In re Buting, 163 USPQ 689 (CCPA 1969) is on point and more applicable to the instant claims wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers. The judges in that case indicated that "We are not aware of any reputable

authority which would accept appellant's two clinical cases as establishing utility for treatment of cancer in humans. As was pointed out in Brenner v. Manson, 148 USPQ 689, a process to be patentable must produce a useful result and be of substantial utility not merely of scientific interest or for further testing. In this case further testing seems necessary".

In summary, applicants have not provided any evidence of record that the instantly claimed compounds can effectively be used in the treatment of all proliferative diseases in general and therefore, it is maintained that one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims. Hence, this rejection is proper and is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 11/078,681. Although the conflicting claims are not identical, they are not patentably distinct from each other because the genus of compounds with the currently elected subject matter, composition and method of use embraced in the instant claims are also embraced in the genus of compounds, composition and method of use of earlier filed copending application 11/078,681. Thus, it would be obvious to one trained in the art to make compounds of the genus of the copending application and expect these compounds including instant compounds to have use recited therein.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

This rejection is same as made in the previous office action. Applicants have differed addressing the issue till all claims are indicated as allowable. For reasons stated above, this rejection is proper and is maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

/Venkataraman Balasubramanian/

Primary Examiner, Art Unit 1624